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(54) ALIPHATIC N-SUBSTITUTED TERTIARY AMIDES POSSESSING PHYSIOLOGICAL COOLING ACTIVITY

(71) We, WILKINSON SWORD LIMITED, of Sword House, High Wycombe, Buckinghamshire (formerly of Sword Works, Southfield Road, London, W.4), a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to compounds having a physiological cooling effect on the skin and on the mucous membranes of the body, particularly the mucous membranes of the nose and bronchial tract.

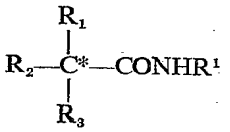
Menthol is well known for its physiological cooling effect on the skin and mucous membranes of the mouth and has been extensively used as a flavouring agent (menthol being a major constituent of oil of peppermint) in for example foodstuffs, beverages, dentrifices and mouthwashes and as a component in a wide range of toiletries, liniments and lotions for topical application. Menthol is also a well known tobacco additive for producing a "cool" sensation in the mouth when smoking. Carvomenthol has also been reported as having a physiological cooling effect and so also have N,N-dimethyl-2-ethyl-butanamide and N,N-diethyl-2-ethyl-butanamide, see French Patent Specification No. 1,572,332.

It is well established that the "cooling" effect of methanol is a physilogical effect due to the direct action of menthol on the nerve ending of the human body responsible for the detection of hot or cold and is not due to latent heat of evaporation. It is believed that the menthol acts as a direct stimulus on the cold receptors at the nerve endings which in turn stimulate the central nervous system.

Although menthol is well established as a physiological coolant its use, in some compositions, is circumscribed by its strong minty odour.

The present invention is based on the discovery that certain other organic compounds, which can be readily synthesised, have a physiological cooling effect similar to that obtained with menthol, but do not have the strong minty odour. In many cases the compounds have little or no odour at all. Such compounds therefore find utility as additives in a wide range of ingestible and topical compositions. More particularly they find utility as components in compositions for nasal application and in vapour rubs and liniments.

The compounds having a physiological cooling effect and provided in accordance with the present invention are amides of the formula:



where

R_1, R_2 and R_3 are each C_1—C_5 alkyl and together provide a total of at least 5 carbon atoms, preferably from 5—10;

R^1 is C_1—C_5 alkyl, C_1—C_8 hydroxyalkyl or alkoxycarbonylalkyl of up to 6 carbon atoms. Preferably R_1 is methyl, ethyl or *n*-propyl and one or both of R_2 and R_3 is branched in an alpha or beta position relative to the carbon atom marked *.

The amides of this invention may readily be prepared by conventional techniques, for example, by reaction of an acid chloride of the formula $R_1R_2R_3COCl$ with an amine of the formula H_2NR^1 in the presence of a hydrogen chloride acceptor. Such reactions are entirely conventional and the procedures involved will readily be understood by persons skilled in the art.

Typical amides according to this invention are listed below in the Table together with an indication of the cooling activity; the more stars the greater the activity, i.e. the greater the degree of cooling produced by a given quantity of the compound.

TABLE

R_1	R_2	R_3	R^1	Activity
CH_3—	iso—C_3H_7—	iso—C_3H_7	C_2H_5—	* * * * *
CH_3—	iso—C_3H_7—	iso—C_3H_7	iso—C_3H_7—	* * * * *
CH_3—	iso—C_3H_7—	iso—C_3H_7	CH_3—	* * * * *
CH_3—	iso—C_3H_7—	iso—C_3H_7	$HOCH_2C(CH_3)_2$—	* * * * *
CH_3—	iso—C_3H_7—	iso—C_3H_7	tert—C_4H_9—	* * * * *
C_2H_5—	C_2H_5—	iso—C_3H_7	C_2H_5—	* * * * *
CH_3—	iso—C_3H_7—	iso—C_4H_9—	C_2H_5—	* * * * *
C_2H_5—	iso—C_3H_7—	iso—C_3H_7—	C_2H_5—	* * * * *
CH_3—	sec—C_4H_9—	sec—C_4H_9—	C_2H_5—	* * * * *
CH_3	iso—C_3H_7—	iso—C_3H_7—	$C_2H_5OOCCH_2$—	* * * *
C_2H_5—	C_2H_5—	C_2H_5—	C_2H_5—	* * * *
CH_3—	sec—C_4H_9—	sec—C_4H_9—	iso—C_3H_7—	* * * *
CH_3—	iso—C_3H_7—	n—C_4H_9—	C_2H_5—	* * * *
CH_3—	iso—C_4H_9—	iso—C_4H_9—	C_2H_5—	* * * *
CH_3—	CH_3—	iso—C_4H_9—	C_2H_5—	* * * *
CH_3—	iso—C_3H_7—	iso—C_3H_7—	$C_2H_5OOCCH_2$—	* * *
C_2H_5—	C_2H_5—	C_2H_5—	$HOCH_2C(CH_3)_2$	* * *
CH_3—	secC_4H_9—	sec—C_4H_9—	$HOCH_2CH_2$—	* * *
CH_3—	sec—C_4H_9—	iso—C_4H_9—	C_2H_5—	* * *
CH_3—	C_2H_5—	C_2H_5—	$C_2H_5OOCCH_2$—	*
CH_3—	CH_3—	iso—C_4H_9—	$C_2H_5OOCCH_2$—	*

The compounds of the above formula find utility in a wide variety of manufactured products for consumption by or application to the human body. Typical products into which the compounds of this invention may be incorporated to give a physiological cooling effect upon use are as follows:

1. Edible or potable compositions including alcoholic and non-alcoholic beverages, confectionery, chewing gum; cachous; ice cream; jellies;
2. Toiletries including after shave lotions, shaving soaps, creams and foams, toilet water, deodorants and anti-perspirants, "solid colognes", toilet soaps, bath oils and salts, shampoos, hair oils, talcum powders, face creams, hand creams, sunburn lotions, cleansing tissues, dentifrices, toothpicks, mouthwashes, hair tonics, eyedrops;
3. Medicaments including antiseptic ointments, pile ointments, liniments, lotions, decongestants, counter-irritants, cough mixtures, throat lozenges, antacid and indigestion preparations, oral analgesics;
4. Tobacco preparations including cigars, cigarettes, pipe tobacco, chewing tobacco and snuff; tobacco filters, especially filter tips for cigarettes;
5. Miscellaneous compositions such as water soluble adhesive compositions for envelopes, postage stamps and adhesive labels.

The compounds of this invention will be incorporated into such products in an amount sufficient to stimulate the cold receptors in the areas of the skin or mucous membrane with which the products (or the smoke therefrom, in the case of tobacco) come into contact during use and thereby promote the desired cold sensation. As the degree and longevity of cooling sensation varies from compound to compound the quantity of stimulant used in each composition will vary widely. As a guide, it may be said that, with the more active compounds, a significant cooling sensation, which, in some cases, may persist for several hours, is achieved upon application to the skin of as little as 0.05 ml. of a 1.0% weight percent solution of the active ingredient in ethanol. For the less active compounds a significant cooling effect is achieved only with more concentrated solutions, e.g. 5% by weight of the active ingredient.

The formulation of such products is described in more detail in our copending Application No. 17914/72 (Serial No. 1,421,743) from which the present application is divided and to which attention is hereby directed.

The following Examples illustrate the preparation of the novel compounds of this invention. All temperatures are in degrees Centigrade. The tertiary carboxylic acid starting materials were obtained by alkyla-

tion of nitriles by known techniques followed by hydrolysis.

EXAMPLE I

Preparation of N-Ethyl-2,3-Dimethyl-2-Isopropylbutanamide

2,3-Dimethyl-2-isopropylbutanoic acid (22 g) was heated under reflux with thionyl chloride (50 ml) for 60 minutes. The excess of thionyl chloride was removed under reduced pressure and the 2,3-dimethyl-2-isopropylbutanoyl chloride was distilled, bp. 73—5°/15 mm.

A portion (2 g) of the acid chloride in diethyl ether (20 ml) was added dropwise to a stirred solution of ethylamine (5 ml of a 70% solution in water) in diethyl ether (100 ml). The mixture was stirred for 1 hour. The ether layer was then washed with water, dilute hydrochloric acid and water. The dried ($MgSO_4$) ether solution was concentrated, and the residue distilled to give N-ethyl - 2,3 - dimethyl - 2 - isopropylbutanamide, bp. 93—5°/1.5 mm, as a colourless liquid which rapidly solidified to a colourless solid mp. 38—40°.

Analysis: Found C: 64.0; H: 10.3; N: 5.9
Calculated C: 64.2; H: 10.3; N: 5.8%

EXAMPLE II

Preparation of N,2,3-Trimethyl-2-Isopropylbutanamide

The procedure of Example I was repeated using methylamine in place of ethylamine. N,2,3-Trimethyl-2-isopropylbutanamide was obtained as a colourless solid, mp. 58—61°, bp. 83—5°/0.35 mm.

EXAMPLE III

Preparation of N-(2,3-Dimethyl-2-Isopropylbutanoyl)-Glycine Ethyl Ester

Sodium bicarbonate (1.7 g, 0.02 mole) and glycine ethyl ester hydrochloride (1.4 g, 0.01 mole) were dissolved in water (10 ml) and a solution of 2,3-dimethyl-2-isopropylbutanoyl chloride (1.6 g, 0.009 mole) in diethyl ether (10 ml) was added. The mixture was stirred vigorously at room temperature for 2 hours. After 16 hours at room temperature the ether layer was separated and dried ($MgSO_4$). Removal of the solvent left a white solid which was recrystallised from diethyl ether/petroleum ether to give N-(2,3-dimethyl-2-isopropylbutanoyl)glycine ethyl ester, mp. 74.5—75.5°.

EXAMPLE IV

Preparation of N-(1,1-Dimethyl-2 Hydroxyethyl)-2,2-Diethylbutanamide

2,2-Diethylbutanoyl chloride was prepared from 2,2-diethylbutanoic acid and thionyl chloride in the usual way.

A solution of this acid chloride (1.2 g) in diethyl ether (30 ml) was added to a stirred solution of 2-amino-2-methylpropan-1-ol (4.0 g) in diethyl ether (90 ml). After 4 hours the ethereal solution was washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and concentrated. The residue was distilled to give N-(1,1-dimethyl-2-hydroxyethyl)-2,2-diethylbutanamide, np. 113—5°/0.9 mm, mp. 57—8°.

Analysis: Found C: 67.5; H: 12.0; N: 6.6
Calculated C: 67.0; H: 11.6; N: 6:5

EXAMPLE V

Preparation of N-Ethyl-2-Isobutyl-2,4-Dimethylpentanamide

2-Isobutyl-2,4-dimethylpentanoyl chloride (bp. 97—100°/16 mm) was prepared in the usual way from 2-isobutyl-2,4-dimethylpentanoic acid (prepared by the alkylation of ethyl cyanide with 2 equivalents of isobutyl bromide, followed by hydrolysis) and thionyl chloride. A solution of the acid chloride (1.5 g) in diethyl ether (20 ml) was added with stirring to a solution of ethylamine (5 ml of a 70% solution in water) in diethyl ether (100 ml). After stirring for 2 hours the ethereal layer was washed with dilute hydrochloric acid and water. The dried ($MgSO_4$) ether solution was concentrated and the residue was recrystallised from petroleum ether (bp. 40—60°) to give N-ethyl - 2 - isobutyl - 2,4 - dimethylpentanamide, mp. 71.5—72.5°.

Analysis: Found C: 72.9; H: 12.3; N: 6.9
Calculated C: 73.3; H: 12.8; N: 6.6%

EXAMPLE VI

Preparation of N-Isopropyl-2-Sec-Butyl-2,3-Dimethylpentanamide

2-Sec-butyl-2,3-dimethylpentanoyl chloride (bp. 108—110°/17 mm) was prepared in the usual way from 2-sec-butyl-2,3-dimethylpentanoic acid and thionyl chloride. A solution of this acid chloride (2.0 g) in diethyl ether (30 ml) was added with stirring to a solution of isopropylamine (2.0 g) in diethyl ether (100 ml). After 16 hours the ethereal

solution was washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and concentrated to give a white solid. This solid was recrystallised from petroleum ether (bp. 40—60°) to give N-isopropyl-2-sec-butyl-2,3-dimethylpentanamide, mp. 74—6°.

Analysis: Found C: 74.3; H: 13.1; N: 6.2
Calculated C: 74.0; H: 12.8; N: 6.2%

EXAMPLE VII

Preparation of N-(2-Hydroxyethyl)-2-Sec-Butyl-2,3-Dimethylpentanamide

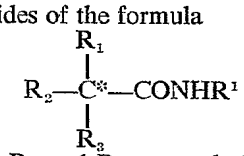
A solution of 2-sec-butyl-2,3-dimethylpentanoyl chloride (2.0 g) in benzene (10 ml) was added to a stirred solution of ethanolamine (2.0 g) in benzene (100 ml). After 16 hours the benzene solution was washed with dilute hydrochloric acid and water, dried ($MgSO_4$) and concentrated to give a pale yellow syrup. Distillation of this syrup gave N - (2 - hydroxyethyl) - 2 - sec-butyl - 2,3-dimethylpentanamide bp. 125—130°/0.03 mm which slowly solidified on standing.

Analysis: Found C: 68.6; H: 11.6; N: 6.3
Calculated C: 68.2; H: 11.8; N: 6.1%

The other compounds listed hereinbefore in the Table were prepared by similar techniques.

WHAT WE CLAIM IS:—

1. Amides of the formula



where R_1, R_2 and R_3 are each C_1—C_5 alkyl and together provide a total of at least 5 carbon atoms;
and R^1 is C_1—C_5 alkyl, C_1—C_3 hydroxyalkyl or alkoxycarbonylalkyl of up to 6 carbon atoms.

2. Amides according to claim 1, where R_1 is methyl, ethyl or *n*-propyl and one or both of R_2 and R_3 is branched at an alpha or beta-position relative to the carbon atom marked (*).

3. Amides according to claim 1, being those amides listed hereinbefore in the Table.

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